IN THE SPECIFICATION:

Please amend paragraph **[0008]** as follows:

[0008] Previously described polymer compositions for injectable implants have used solvent/plasticizers that are very or relatively soluble in aqueous body fluids to promote rapid solidification of the polymer at the implant site and promote diffusion of drug from the implant. Rapid migration of water into such polymeric implants utilizing water soluble polymer solvents when the implants are placed in the body and exposed to aqueous body fluids presents a serious problem. The rapid water uptake often results in implants having pore structures that are nonhomogeneous in size and shape. Typically, the surface pores take on a finger-like pore structure extending for as much as one-third of a millimeter or more from the implant surface into the implant, and such finger-like pores are open at the surface of the implant to the environment of use. The internal pores tend to be smaller and less accessible to the fluids present in the environment of use. The rapid water uptake characteristic often results in uncontrolled release of beneficial agent that is manifested by an initial, rapid release of beneficial agent from the polymer composition, corresponding to a "burst" of beneficial agent being released from the implant. The burst often results in a substantial portion of the beneficial agent, if not all, being released in a very short time, e.g., hours or 1-2 days. Such an effect can be unacceptable, particularly in those circumstances where a controlled delivery is desired, i.e., delivery of beneficial agent in a controlled manner over a period of greater than or equal to a month or up to one year, or where there is a narrow therapeutic window and release of excess beneficial agent can result in adverse consequences to the subject being treated, or where it is necessary to mimic the ~~naturally occurring~~ naturally occurring daily profile of beneficial agents, such as hormones and the like, in the body of the subject being treated.

Please amend paragraph **[0020]** as follows:

[0020] In another aspect, the invention pertains to an injectable depot composition as described above, wherein the viscous gel further comprises a polymer, such as a biodegradable polymer, selected from the group consisting of polylactides, polyglycolides, caprolactone-based polymers, ~~poly (caprolactone),~~ poly(caprolactone), polyanhydrides, polyamines,

polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyphosphoesters, polyesters, polybutylene terephthalate, polyorthocarbonates, polyphosphazenes, succinates, poly(malic acid), poly(amino acids), polyvinylpyrrolidone, polyethylene glycol, polyhydroxycellulose, polysaccharides, chitin, chitosan, hyaluronic acid, and copolymers, terpolymers and mixtures thereof.

Please amend paragraph **[0022]** as follows:

[0022] In preferred embodiments, the solvent is selected from the aromatic alcohol, lower alkyl and aralkyl esters of aryl acids; aryl, aralkyl and lower alkyl ketones; and lower alkyl esters of citric acid. Preferably, the solvent is selected from benzyl alcohol, benzyl benzoate and ethyl benzoate. In preferred embodiments, the composition is free of solvents having a miscibility in water that is greater than 7 wt.% at 25° C. Preferably the solvent has a miscibility in water of less than 7 wt.%, more preferably less than ~~5 wt.%,~~ 5 wt.%, and even more preferably less than ~~3 wt.%.~~ 3 wt.%.

Please amend paragraph **[0042]** as follows:

[0042] Figure 13 is a graph illustrating the *in vivo* release profile of leuprolide acetate obtained from the depot formulations of the present invention (formulations 42 and 47) as compared with 3-month ~~Lupron depot®~~ LUPRON DEPOT® (formulation 53).

Please amend paragraph **[0045]** as follows:

[0045] Figure 16 is a graph illustrating the *in vivo* release profile of leuprolide acetate obtained from the depot formulation of the present invention (formulation 46) as compared with 3-month ~~Lupron depot®~~ LUPRON DEPOT® (formulation 53).

Please amend paragraph **[0046]** as follows:

[0046] Figure 17 is a graph illustrating the *in vivo* release profile of leuprolide acetate obtained from the depot formulation of the present invention (formulations 42, 51 and 52) as compared with 3-month ~~Lupron depot®~~ LUPRON DEPOT® (formulation 53).

Please amend paragraph **[0061]** as follows:

[0061] When the composition is intended for implantation by injection, the viscosity optionally may be modified by addition of emulsifiers or thixotropic agents to obtain a gel composition having a viscosity low enough to permit passage of the gel composition through a needle. Also, pore formers and solubility modulators of the beneficial agent may be added to the implant systems to provide desired release profiles from the implant systems, along with typical pharmaceutical excipients and other additives that do not change the beneficial aspects of the present invention. The addition of a solubility modulator to the implant system may enable the use of a solvent having a solubility of 7% or greater by weight in the implant system with minimal burst and sustained delivery under particular circumstances. However, it is presently preferred that the implant system utilize at least one solvent having a solubility in water of less than 7% by weight, whether the solvent is present alone or as part of a solvent mixture. It has also been discovered that when mixtures of solvents which include a solvent having 7% or less by weight solubility in water and one or more miscible solvents, optionally having greater solubility, are used, implant systems exhibiting limited water uptake and minimal burst and sustained delivery characteristics are obtained.

Please amend paragraph **[0067]** as follows:

[0067] The term "systemic" means, with respect to delivery or administration of a beneficial agent to a subject, that the beneficial agent is detectable at a ~~biologically significant~~ biologically significant level in the blood plasma of the subject.

Please amend paragraph **[0089]** as follows:

[0089] Typically, the viscous gel will be injected from a standard hypodermic syringe through a needle, a catheter, or a trocar, that has been prefilled with the beneficial agent-viscous gel composition to form the depot. It is often preferred that injections take place using the smallest size needle (i.e., smallest diameter) to reduce discomfort to the subject when the injection is in a subcutaneous, intramuscular, intravascular (high/low flow), intramyocardial,

adventitial, intratumoral, or intracerebral portion, wound ~~sites,~~ site, tight joint ~~spaces~~ space or body cavity of a human or animal. It is desirable to be able to inject gels through a needle or a catheter ranging from 16 gauge and higher, preferably 20 gauge and higher, more preferably 22 gauge and higher, and even more preferably 24 gauge and higher. With highly viscous gels, i.e., gels having a viscosity of about 200 poise or greater, injection forces to dispense the gel from a syringe having a needle in the 20-30 gauge range may be so high as to make the injection difficult or reasonably impossible when done manually. At the same time, the high viscosity of the gel is desirable to maintain the integrity of the depot after injection and during the dispensing period and also to facilitate desired suspension characteristics of the beneficial agent in the gel.

Please amend paragraph **[0099]** as follows:

[0099] (E) Polymers with different molecular weight, end group and comonomer ratios: Depot gel compositions having a blend of polymers having different molecular weight, end group and comonomer ratios result in a depot formulation having a lower burst index and a regulated duration of delivery. For example, blending LMW PLGA (L/G : 50/50) and PLGA RG502H (acid end group) with PLGA RG502 (ester end group) would yield a depot gel composition having a lower burst index (as compared to a gel composition having PLGA RG502 alone) and a duration of delivery of about one month. Blending LMW PLGA (L/G : 50/50) and PLGA RG503H (acid end group) with PLGA RG752 (ester end group) would yield a depot gel composition having a lower burst index (as compared to a gel composition having PLGA RG752 alone) and a duration of delivery of about 3 months to about 4 months after administration. Blending LMW PLGA (L/G : 50/50) and PLGA RG755H (acid end group) with PLA R202 (ester end group) would yield a depot gel composition having a lower burst index (as compared to a gel composition having PLA 202 alone) and a duration of delivery greater than or equal to 6 months after administration. Blending PLGA RG502H (acid end group) and PLGA RG752 (ester end group) with PLA R206 (ester end group) would yield a depot gel composition having a lower burst index (as compared to a gel composition having PLA 202 alone) and a duration of delivery greater than or equal to 6 months after administration.

Please amend paragraph **[00105]** as follows:

[00105] Preferably, the polymer matrix comprises about 0 wt.% to about 95 wt.% of ~~LWM~~ LMW polymer, preferably about 20 wt.% to about 90 wt.% of LMW polymer, more preferably about 30 wt.% to about 80 wt.% of LMW polymer, and more preferably about 40 wt.% to about 75 wt.% of LMW polymer; about 0 wt.% to about 50 wt.% of HMW polymer, preferably about 5 wt.% to about 40 wt.% of HMW polymer, more preferably about 10 wt.% to about 30 wt.% of HMW polymer, and more preferably about 15 wt.% to about 25 wt.% of HMW polymer; and about 0 wt.% to about 95 wt.% of MMW polymer, preferably about 20 wt.% to about 90 wt.% of MMW polymer, more preferably about 30 wt.% to about 80 wt.% of MMW polymer, and more preferably about 40 wt.% to about 65 wt.% of MMW polymer.

Please amend paragraph **[00109]** as follows:

[00109] Examples of polymers include, but are not limited to, Poly (D,L-lactide-co-glycolide) 50:50 ~~Resomer®~~ RESOMER® RG502, Poly (D,L-lactide-co-glycolide) 50:50 ~~Resomer®~~ RESOMER® RG502H, Poly D,L Lactide ~~(Resomer® R 202, Resomer®~~ (RESOMER® R202, RESOMER® R203); Poly dioxanone ~~(Resomer®~~ (RESOMER® X 210) (Boehringer Ingelheim Chemicals, Inc., Petersburg, VA). Additional examples include, but are not limited to, DL-lactide/glycolide 100:0 (MEDISORB® Polymer 100 DL High, MEDISORB® Polymer 100 DL Low); DL-lactide/glycolide 85/15 (MEDISORB® Polymer 8515 DL High, MEDISORB® Polymer 8515 DL Low); DL-lactide/glycolide 75/25 (MEDISORB® Polymer 7525 DL High, MEDISORB® Polymer 7525 DL Low); DL-lactide/glycolide 65/35 (MEDISORB® Polymer 6535 DL High, MEDISORB® Polymer 6535 DL Low); DL-lactide/glycolide 54/46 (MEDISORB® Polymer 5050 DL High, MEDISORB® Polymer 5050 DL Low); and DL-lactide/glycolide 54/46 (MEDISORB® Polymer 5050 DL 2A(3), MEDISORB® Polymer 5050 DL 3A(3), MEDISORB® Polymer 5050 DL 4A(3)) (Medisorb Technologies International L.P., Cincinnati, OH); and Poly D,L-lactide-co-glycolide 50:50; Poly D,L-lactide-co-glycolide 65:35; Poly D,L-lactide-co-glycolide 75:25; Poly D,L-lactide-co-glycolide 85:15; Poly DL-lactide; Poly L-lactide; Poly glycolide; Poly

ε-caprolactone; Poly DL-lactide-co-caprolactone 25:75; and Poly DL-lactide-co-caprolactone 75:25 (Birmingham Polymers, Inc., Birmingham, AL).

Please amend paragraph **[00112]** as follows:

[00112] The solvent must be biocompatible, should form a viscous gel with the polymer, and restrict water uptake into the implant. The solvent may be a single solvent or a mixture of solvents exhibiting the foregoing properties. The term "solvent," unless specifically indicated otherwise, means a single solvent or a mixture of solvents. Suitable solvents will substantially restrict the uptake of water by the implant and may be characterized as immiscible in water, i.e., having a solubility in water of less than 7% by weight. Preferably, the solvents are ~~five weight percent~~ 5 wt.% or less soluble in water; more preferably ~~three weight percent~~ 3 wt.% or less soluble in water; and even more preferably ~~one weight percent~~ 1 wt.% or less soluble in water. Most preferably the solubility of the solvent in water is equal to or less than ~~0.5 weight percent.~~ 0.5 wt.%.

Please amend paragraph **[00113]** as follows:

[00113] Water miscibility may be determined experimentally as follows: Water (1-5 g) is placed in a tared clear container at a controlled temperature, about 20° C, and weighed, and a candidate solvent is added dropwise. The solution is swirled to observe phase separation. When the saturation point appears to be reached, as determined by observation of phase separation, the solution is allowed to stand overnight and is rechecked the following day. If the solution is still saturated, as determined by observation of phase separation, then the percent (w/w) of solvent added is determined. Otherwise more solvent is added and the process is repeated. Solubility or miscibility is determined by dividing the total weight of solvent added by the final weight of the solvent/water mixture. When solvent mixtures are used, for ~~example~~ example, 20% triacetin and 80% benzyl benzoate, they are premixed prior to adding to the water.

Please amend paragraph **[00118]** as follows:

[00118] In the ketone of formula ~~(III~~ (III) R3 and R4 may be selected from any of the R1 and R2 groups identified above.

Please amend paragraph **[00120]** as follows:

[00120] Art recognized phthalic acid derivatives from which solvents having the requisite solubility may be selected include: Alkyl benzyl phthalate, bis-cumyl-phenyl isophthalate, dibutoxyethyl phthalate, dimethyl phthalate, ~~dimethyl phthalate,~~ diethyl phthalate, dibutyl phthalate, diisobutyl phthalate, butyl octyl phthalate, diisoheptyl phthalate, ~~butyl octyl phthalate,~~ diisononyl phthalate, nonyl undecyl phthalate, dioctyl phthalate, di-isooctyl phthalate, dicapryl phthalate, mixed alcohol phthalate, di-(2-ethylhexyl) phthalate, linear heptyl nonyl phthalate, linear heptyl nonyl undecyl phthalate, linear nonyl phthalate, linear nonyl undecyl phthalate, linear dinonyl, didecyl phthalate (diisodecyl phthalate), diundecyl phthalate, ditridecyl phthalate, undecyldodecyl phthalate, decyltridecyl phthalate, blend (50/50) of dioctyl and didecyl phthalates, butyl benzyl phthalate, and dicyclohexyl phthalate.

Please amend paragraph **[00123]** as follows:

[00123] The composition may also include, in addition to the water-immiscible solvent(s), one or more additional miscible solvents ("component solvents"), provided that any such additional solvent is other than a lower alkanol. Component solvents compatible and miscible with the primary solvent(s) may have a higher miscibility with water and the resulting mixtures may still exhibit significant restriction of water uptake into the implant. Such mixtures will be referred to as "component solvent mixtures." Useful component solvent mixtures may exhibit solubilities in water greater than the primary solvents themselves, typically between ~~0.1 weight percent~~ 0.1 wt.% and up to and including ~~50 weight percent,~~ 50 wt.%, preferably up to and including ~~30 weight percent,~~ 30 wt.%, and most preferably up to and including ~~10 weight percent,~~ 10 wt.%, without detrimentally affecting the restriction of water uptake exhibited by the implants of the invention.

Please amend paragraph **[00135]** as follows:

[00135] Depending on the particular solvent or solvent mixture selected, the polymer and beneficial ~~agent, and optionally~~ agent and, optionally, solubility modulators of the beneficial agent, the compositions of the present invention intended for systemic delivery may provide a gel composition having a burst index of 8 or less, preferably 6 or less, more preferably 4 or less and most preferably 2 or less. Compositions of PLGA with an average molecular weight ranging from about 3,000 to about 120,000 are desired; preferably from about 7,000 to about 100,000; more preferably from about 10,000 to about 80,000; and more preferably the polymer has a molecular weight of about 14,000 to about 60,000, with solvents having a miscibility in water of less than 7% by weight, optionally combined with the other solvents, providing implants intended for systemic delivery of beneficial agent having a burst index of 10 or less, preferably 7 or less, more preferably 5 or less and most preferably 3 or less, are particularly advantageous. The use of solvent mixtures as discussed herein can be particularly advantageous as a means of providing sufficient plasticizing of the polymer to obtain viscous gel formation and at the same time meet the desired burst indices and percentage release objectives of the compositions of the invention.

Please amend paragraph **[00138]** as follows:

[00138] The gel formed by mixing the polymer and the solvent typically exhibits a viscosity of from about 100 to about 50,000 poise, preferably from about 500 to about 30,000 poise, more preferably from about 500 to about 10,000 poise measured at a 1.0 sec^{-1} shear rate and 25° C using a Haake Rheometer at about 1-2 days after mixing is completed. Mixing the polymer with the solvent can be achieved with conventional low shear equipment such as a Ross double planetary mixer for from about 10 minutes to about 1 hour, although shorter and longer periods may be chosen by one skilled in the art depending on the particular physical characteristics of the composition being prepared. Since the depot gel composition of the invention is administered as an injectable composition, a countervailing consideration when forming depot gel compositions that are viscous gels is that the polymer/solvent/ beneficial agent composition have sufficiently low viscosity in order to permit it to be forced through a small

diameter, e.g., ~~18-20 gauge~~ 18- to 20-gauge needle. If necessary, adjustment of viscosity of the gel for injection can be accomplished with emulsifying agents as described herein. Yet, such compositions should have adequate dimensional stability so as to remain localized and be able to be removed if necessary. The particular gel or gel-like compositions of the present invention satisfy such requirements.

Please amend paragraph **[00139]** as follows:

[00139] If the polymer composition is to be administered as an injectable gel, the level of polymer dissolution will need to be balanced with the resulting gel viscosity, to permit a reasonable force to dispense the viscous gel from a needle or a catheter, and the potential burst effect. Highly viscous gels enable the beneficial agent to be delivered without exhibiting a significant burst effect, but may make it difficult to dispense the gel through a needle or a catheter. In those instances, an emulsifying agent may optionally be added to the composition. Also, since the viscosity may generally be lowered as the temperature of the composition increases, it may be advantageous in certain applications to reduce the viscosity of the gel by heating to provide a more readily injectable composition. The shear thinning characteristics of the depot gel compositions of the present invention allow them to be readily injected into an ~~animal including humans~~ animal, including humans, using standard gauge needles or catheters without requiring undue dispensing pressure.

Please amend paragraph **[00144]** as follows:

[00144] The beneficial agent can be any physiologically or pharmacologically active substance or substances optionally in combination with pharmaceutically acceptable carriers and additional ingredients such as antioxidants, stabilizing agents, permeation enhancers, ~~etc.~~ etc., that do not substantially adversely affect the advantageous results that can be attained by the present invention. The beneficial agent may be any of the agents which are known to be delivered to the body of a human or an animal and that are preferentially soluble in water rather than in the polymer-dissolving solvent. These agents include drug agents, medicaments, vitamins, nutrients, or the like. Included among the types of agents which meet this description

are lower molecular weight compounds, proteins, peptides, genetic material, nutrients, vitamins, food supplements, sex sterilants, fertility inhibitors and fertility promoters.

Please amend paragraph **[00146]** as follows:

[00146] Examples of drugs which may be delivered by the composition of the present invention include, but are not limited to bupivacaine, buprenorphine, prochlorperzine edisylate, ferrous sulfate, aminocaproic acid, mecamylamine hydrochloride, procainamide hydrochloride, amphetamine sulfate, methamphetamine hydrochloride, benzamphetamine hydrochloride, isoproterenol sulfate, phenmetrazine hydrochloride, bethanechol chloride, methacholine chloride, pilocarpine hydrochloride, atropine sulfate, scopolamine bromide, isopropamide iodide, tridihexethyl chloride, phenformin hydrochloride, methylphenidate hydrochloride, theophylline cholinate, cephalexin hydrochloride, diphenidol, meclizine hydrochloride, prochlorperazine maleate, phenoxybenzamine, thiethylperzine maleate, anisindone, diphenadione erythrityl tetranitrate, digoxin, isoflurophate, acetazolamide, methazolamide, bendroflumethiazide, chloropromaide, tolazamide, chlormadinone acetate, phenaglycodol, allopurinol, aluminum aspirin, methotrexate, acetyl sulfisoxazole, erythromycin, hydrocortisone, hydrocorticosterone acetate, cortisone acetate, dexamethasone and its ~~derivatives~~ derivatives, such as betamethasone, triamcinolone, methyltestosterone, testosterone, 17-S-estradiol, ethinyl estradiol, ethinyl estradiol 3-methyl ether, prednisolone, 17α-hydroxyprogesterone acetate, 19-nor-progesterone, norgestrel, norethindrone, norethisterone, norethiederone, progesterone, norgesterone, norethynodrel, aspirin, indomethacin, naproxen, fenoprofen, sulindac, indoprofen, nitroglycerin, isosorbide dinitrate, propranolol, timolol, atenolol, alprenolol, cimetidine, clonidine, imipramine, levodopa, chlorpromazine, methyldopa, dihydroxyphenylalanine, theophylline, calcium gluconate, ketoprofen, ibuprofen, cephalexin, erythromycin, haloperidol, zomepirac, ferrous lactate, vincamine, diazepam, phenoxybenzamine, diltiazem, milrinone, mandol, quanbenz, hydrochlorothiazide, ranitidine, flurbiprofen, fenufen, fluprofen, tolmetin, alclofenac, mefenamic, flufenamic, difuinal, nimodipine, nitrendipine, nisoldipine, nicardipine, felodipine, lidoflazine, tiapamil, gallopamil, amlodipine, mioflazine, ~~lisinolpril,~~ lisinopril, enalapril, enalaprilat, captopril, ramipril, famotidine, nizatidine, sucralfate, etintidine, tetratolol, minoxidil,

chlordiazepoxide, ~~diazepam,~~ amitriptyline, ~~imipramine,~~ paliperidone, resperidone, octreotide, alendronate, α-4,β^{-7} receptor antagonist leukocyte and infliximab ~~(Remicade).~~ (REMICADE®). Further examples are proteins and peptides which include, but are not limited to, bone morphogenic proteins, insulin, colchicine, glucagon, thyroid stimulating hormone, parathyroid and pituitary hormones, calcitonin, renin, prolactin, corticotrophin, thyrotropic hormone, follicle stimulating hormone, chorionic gonadotropin, gonadotropin releasing hormone, bovine somatotropin, porcine somatotropin, oxytocin, vasopressin, GRF, somatostatin, lypressin, pancreozymin, luteinizing hormone, LHRH, LHRH agonists and antagonists, leuprolide, interferons such as interferon alpha-2a, interferon alpha-2b, and consensus interferon, interleukins, growth hormones such as human growth hormone and its derivatives such as methione-human growth hormone and des-phenylalanine human growth hormone, parathyroid hormone, bovine growth hormone and porcine growth hormone, fertility inhibitors such as the prostaglandins, fertility promoters, growth factors such as epidermal growth factors (EGF), platelet-derived growth factors (PDGF), fibro-blast growth factors (FGF), transforming growth factors-α (TGF-α), transforming growth factors-β (TGF-β), erythropoietin (EPO), insulin-like growth factor-I-(IGF-I), insulin-like growth factor-II (IGF-II), interleukin-1, interleukin-2, interleukin-6, interleukin-8, tumor necrosis factor-α (TNF-α), tumor necrosis factor-β (TNF-β), Interferon-α (INF-α), Interferon-β (INF-β), Interferon-γ (INF-γ), Interferon-ω (INF-ω), colony stimulating factors ~~(CGF),~~ (CSF), vascular cell growth factor (VEGF), thrombopoietin (TPO), stromal cell-derived factors (SDF), placenta growth factor (PIGF), hepatocyte growth factor (HGF), granulocyte macrophage colony stimulating factor (GM-CSF), glial-derived neurotropin factor (GDNF), granulocyte colony stimulating factor (G-CSF), ciliary neurotropic factor (CNTF), bone growth factor, transforming growth factor, bone morphogeneic proteins (BMP), coagulation factors, human pancreas hormone releasing factor, analogs and derivatives of these compounds, and pharmaceutically acceptable salts of these compounds, or their analogs or derivatives.

Please amend paragraph **[00151]** as follows:

[00151] The beneficial agent is typically dissolved or dispersed in the composition in an amount of from about 0.1 to about 70% by weight, preferably in an amount of from about 0.5 to about 50% and often 1 to 30% by weight of the combined amounts of the polymer, solvent and beneficial agent. Depending on the amount of beneficial agent present in the composition, one can obtain different release profiles and burst indices. More specifically, for a given polymer and solvent, by adjusting the amount of these components and the amount of the beneficial agent, one can obtain a release profile that depends more on the degradation of the polymer than the diffusion of the beneficial agent from the composition or vice versa. In general, during the early stages, the release rate profile is generally controlled by the rate of diffusion and the rate of dissolution of the beneficial agent from the composition; while in the later stages, polymer degradation is the major factor in determining the release rate profiles. In this respect, at lower beneficial agent loading level, the release profile depends primarily on the rate of degradation of the polymer, and secondarily on the diffusion of the beneficial agent from the composition, wherein generally the release rate increases or is constant (e.g., flat profile) ~~with time.~~ with time.

Please amend paragraph **[00154]** as follows:

[00154] Release rates and loading of beneficial agent will be adjusted to provide for ~~therapeutically effective~~ therapeutically effective delivery of the beneficial agent over the intended sustained delivery period. Preferably, the beneficial agent will be present in the polymer gel at concentrations that are above the saturation concentration of beneficial agent in water to provide a drug reservoir from which the beneficial agent is dispensed. While the release rate of beneficial agent depends on the particular circumstances, such as the beneficial agent to be administered, release rates on the order of from about 0.1 to about 10,000 micrograms/day, preferably from about 1 to about 5,000 micrograms per day, for periods of from about 2 weeks to about one year can be obtained. Greater amounts may be delivered if delivery is to occur over shorter periods. Generally, a higher release rate is possible if a greater burst can be tolerated. In instances where the gel composition is surgically implanted, or used as a "leave behind" depot when surgery to treat the disease state or another condition is concurrently conducted, it is

possible to provide higher doses than would normally be administered if the implant was injected. Further, the dose of beneficial agent may be controlled by adjusting the volume of the gel implanted or the injectable gel injected.

Please amend paragraph **[00155]** as follows:

[00155] Figures ~~6A-D~~ 6A-6D and 7-21 illustrate representative release profiles of various beneficial agents obtained in rats from preferred compositions of this invention. As illustrated in the figures, the injectable depot gel formulations of the invention comprising polymers provide a controlled, sustained release of a beneficial agent over a specified/desired duration of time. The duration and the release rate profiles can be adjusted depending on the nature of the polymer and the properties of the polymer ~~(e.g.,~~ (e.g., MW, comonomer ratios, end-group), and the nature of the solvent and the polymer/solvent ratio.

Please amend paragraph **[00157]** as follows:

[00157] The thixotropic agent, i.e., an agent that imparts thixotropic properties to the polymer gel, is selected from the lower alkanols. Lower alkanol means an alcohol that contains 2-6 carbon atoms and is straight chain or branched chain. Such alcohols may be exemplified by ethanol, isopropanol, and the like. Importantly, such a thixotropic agent is not a polymer solvent. (See, e.g., *Development of an in situ forming biodegradable poly-lactide-co-glycolide system for controlled release of proteins,* Lambert, W.J., and Peck, K.D., *Journal of Controlled Release,* ~~33 (1995) 189-195).~~ 33 (1995) 189-195.)

Please amend paragraph **[00162]** as follows:

[00162] A gel vehicle for use in an injectable depot of the composition was prepared as follows. A glass vessel was tared on a Mettler AE 163 analytical balance or a Mettler PJ3000 top loader balance. Poly (D,L-lactide-co-glycolide) (PLGA), (L/G ratio of 50/50) with an inherent viscosity of 0.15 (PLGA-BPI, Birmingham Polymers, Inc., Birmingham, AL); ~~Resomer®~~ RESOMER® PLGA RG502 (L/G ratio of 50/50), ~~Resomer®~~ RESOMER® PLGA RG503 (L/G ratio of 50/50); 50:50 ~~Resomer®~~ RESOMER® RG504 (PLGARG 504); or a Poly

(D,L-lactide-co-glycolide) (PLGA) (L/G ratio of 75/25, ~~Resomer®~~ RESOMER® RG752 (Boehringer ~~Ingelheim~~ Ingelheim Chemicals Inc., Petersburg, VA), were milled and sieved below 425 microns. The polymer was weighed into the glass vessel. The glass vessel containing the polymer was tared and the corresponding solvent was added. Amounts expressed as percentages for various polymer/solvent combinations are set forth in Table 1, below. The polymer/solvent mixture was stirred at 250 ± 50 rpm (IKA electric stirrer, IKH-Werke GmbH and Co., Stanfen, Germany) for about ~~5—10~~ 5 to 10 minutes, resulting in a sticky paste-like substance containing polymer particles. The vessel containing the polymer/solvent mixture was sealed and placed in a temperature-controlled incubator equilibrated to 37° C for 1 to 4 days, with intermittent stirring, depending on the type and/or amount of solvent and polymer. The polymer/solvent mixture was removed from the incubator when it appeared to be a clear amber homogeneous solution. Thereafter, the mixture was placed in an oven (65° C, 30 minutes) until polymer was dissolved in the mixture.

Please amend paragraph **[00163]** and Table 1 (only missing a bottom gridline in 2nd column, 5th row) immediately following it as follows:

[00163] Additional depot gel vehicles are prepared with the following solvents or mixtures of solvents: benzyl benzoate ("BB"), benzyl alcohol ("BA"), ethyl benzoate ("EB"), ethanol, and propylene glycol ("PG"), and mixtures thereof and the following polymers: Poly (D,L-lactide-co-glycolide) 75:25 ~~(Resomer®~~ (RESOMER® RG752), Poly (D,L-lactide-co-glycolide) 75:25 ~~(Resomer®~~ (RESOMER® RG755), Poly (D,L-lactide-co-glycolide) 75:25 ~~(Resomer®~~ (RESOMER® RG756), Poly (D,L-lactide-co-glycolide) 85:15 ~~(Resomer®~~ (RESOMER® RG858), Poly (D,L-lactide) ~~(Resomer®~~ (RESOMER® R104), Poly (D,L-lactide) ~~(Resomer®~~ (RESOMER® R202), Poly (D,L-lactide) ~~(Resomer®~~ (RESOMER® R202H), Poly (D,L-lactide) ~~(Resomer®~~ (RESOMER® R203), Poly (D,L-lactide) ~~(Resomer®~~ (RESOMER® R206), Poly (D,L-lactide) ~~(Resomer®~~ (RESOMER® R207), Poly (D,L-lactide) ~~(Resomer®~~ (RESOMER® R208), Poly L-Lactide-co-D,L-lactide 90:10 ~~(Resomer®~~ (RESOMER® LR 209); Poly ~~(D,L-lactide-co-glycolide)~~ (D,L-lactide-co-glycolide) 50:50 ~~Resomer®~~ RESOMER® RG502; Poly

(D,L-lactide-co-glycolide) 50:50 ~~(Resomer®)~~ RESOMER® RG502H, PLGA-502H; Poly (D,L-lactide-co-glycolide) 50:50 ~~(Resomer®)~~ RESOMER® RG503, PLGA-503; Poly (D,L-lactide-co-glycolide) 50:50 ~~(Resomer®)~~ RESOMER® RG755, PLGA-755; Poly (L-lactide) ~~(Resomer®)~~ (RESOMER® L104), Poly (L-lactide) ~~(Resomer®)~~ (RESOMER® L206), Poly (L-lactide) ~~(Resomer®)~~ (RESOMER® L207), Poly (L-lactide) ~~(Resomer®)~~ (RESOMER® L209), Poly (L-lactide) ~~(Resomer®)~~ (RESOMER® L210), Poly (L-lactide) ~~(Resomer®)~~ (RESOMER® L214), Poly D-L-lactide-co-glycolide 75:25 ~~(Resomer®)~~ (RESOMER® RG 752, ~~Resomer®~~ RESOMER® RG 756); Poly D,L-lactide-co-glycolide 85:15 ~~(Resomer®)~~ (RESOMER® RG 858); Poly L-lactide-co-trimethylene carbonate 70:30 ~~(Resomer®)~~ (RESOMER® LT 706); Poly dioxanone ~~(Resomer®)~~ (RESOMER® X 210) (Boehringer Ingelheim Chemicals, Inc., Petersburg, VA); Poly (L-lactide-co-D,L-lactide) 70:30 ~~(Resomer®)~~ (RESOMER® LR708), Poly (L-Lactide-co-D,L-lactide) 90:10 ~~(Resomer®)~~ (RESOMER® LR 209), Poly(D,L-lactide) (MEDISORB® Polymer 100 DL High, MEDISORB® Polymer 100 DL Low); Poly(D,L-lactide-co-glycolide) 85:15 (MEDISORB® Polymer 8515 DL High, MEDISORB® Polymer 8515 DL Low), Poly(D,L-lactide-co-glycolide) 75:25 (MEDISORB® Polymer 7525 DL High, MEDISORB® Polymer 7525 DL Low), Poly(D,L-lactide-co-glycolide) 65:35 (MEDISORB® Polymer 6535 DL High, MEDISORB® Polymer 6535 DL Low), DL-lactide/glycolide 54/46 (MEDISORB® Polymer 5050 DL High, MEDISORB® Polymer 5050 DL Low); and DL-lactide/glycolide 54/46 (MEDISORB® Polymer 5050 DL 2A(3), MEDISORB® Polymer 5050 DL 3A(3), MEDISORB® Polymer 5050 DL 4A(3)) (Medisorb Technologies International L.P., Cincinnati, OH); and Poly D,L-lactide-co-glycolide 50:50; Poly D,L-lactide-co-glycolide 65:35; Poly (D,L-lactide-co-glycolide) 65:35 (Birmingham Polymers, Inc., Birmingham, AL); Poly (D,L-lactide-co-glycolide) 75:25 (Birmingham Polymers, Inc., Birmingham, AL); Poly (D,L-lactide-co-glycolide) 85:15 (Birmingham Polymers, Inc., Birmingham, AL); Poly D,L-lactide (Birmingham Polymers, Inc., Birmingham, AL); Poly L-lactide (Birmingham Polymers, Inc., Birmingham, AL); Poly glycolide; Poly ε-caprolactone; Poly (D,L-lactide-co-caprolactone) 25:75 (Birmingham Polymers, Inc., Birmingham, AL); and Poly (D,L-lactide-co-caprolactone) 75:25 (Birmingham Polymers, Inc., Birmingham, AL). Representative gel vehicles are described in Tables 1-3 below.

Table 1

Formulation	PLGA (wt%)	BB (wt%)	BA (wt%)
1	50[1a]	50	-
2	50[1a]	37.5	12.5
3	30[1b]	70	-
4	30[1b]	52.5	17.5
5	40[1b]	60	-
6	40[1b]	45	15
7	20[1c]	80	-
8	20[1c]	60	20
9	30[1c]	70	-
10	30[1c]	52.5	17.5

1a = PLGA RG752; lb = PLGA RG755; and 1c = PLGA RG756.

Please amend paragraph **[00165]** as follows:

[00165] Human growth hormone (hGH) particles were prepared as follows: Lyophilized hGH (3.22 grams, Pharmacia-Upjohn, Stockholm, Sweden) and stearic acid (3.22 grams, 95% pure, Sigma-Aldrich Corporation, St. Louis, MO) were blended and ground. The ground material was compressed in a ~~13 mm~~ 13-mm round die, with a force of 10,000 pounds for 5 minutes. Compressed tablets were ground and sieved through a ~~70 mesh~~ 70-mesh screen followed by a 400 mesh screen to obtain particles having a size range between ~~38 – 212~~ 38 and 212 microns.

Please amend paragraph **[00166]** as follows:

[00166] Bupivacaine hydrochloride (Sigma-Aldrich Corporation, St. Louis, MO) was dissolved in deionized (DI) water at a concentration of 40 mg/ml (saturation). A calculated amount of sodium hydroxide (in the form of 1 N solution) was added to the solution and the pH of the final ~~mixtures~~ mixture was adjusted to 10 to precipitate the Bupivacaine base. The precipitated product was filtered, and further washed with DI water at least three times. The precipitated product was dried at ca. 40° C in vacuum for 24 hours.

Please amend paragraph **[00167]** as follows:

[00167] Bupivacaine drug particles (both base and hydrochloride salt) were prepared as follows. Bupivacaine hydrochloride (Sigma-Aldrich Corporation, St. Louis, MO) or bupivacaine base prepared according to Example 4 were grounded and then sieved to a fixed range using ~~3"~~ 3-inch stainless steel sieves. Typical ranges include 25μm to 38μm, 38μm to 63μm, and 63μm to 125μm.

Please amend paragraph **[00168]** as follows:

[00168] Bupivacaine particles were prepared as follows: Bupivacaine hydrochloride (100 grams, Sigma-Aldrich Corporation, St. Louis, MO) was grounded and sieved through 63-125 micron sieves. The bupivacaine particles and stearic acid (100 grams, 95% pure, Sigma-Aldrich Corporation, St. Louis, MO) were blended and ground. The ground material was compressed in a ~~13-mm~~ 13-mm round die, with a force of 5,000 pounds for 5 minutes. Compressed tablets were ground and sieved through a ~~120-mesh~~ 120-mesh screen followed by a ~~230-mesh~~ 230-mesh screen to obtain particles having a size range between 63-125 microns.

Please amend paragraph **[00169]** as follows:

[00169] Leuprolide acetate (Mallinckrodt Inc., St. Louis, MO) was ground and sieved between 63-125μm sieves (for nominal particle size of 90μm). ~~An~~ A GILSON digital Sieve Shaker may be employed to speed the sieving (Gilson Company Inc., Worthington, OH).

Please amend paragraph **[00170]** as follows:

[00170] Stearic acid (95% pure, Sigma-Aldrich Corporation, St. Louis, MO) was passed through a 120-mesh screen (125μm). Equal amounts of milled leuprolide acetate (<63μm, prepared as described in Example 2 above) and sieved stearic acid were transferred to the Waring blender and blended for 30 seconds. The blended materials were compressed in a ~~13-mm~~ 13-mm round die using a compression force of 5,000 lbs and hold time of 5 min. Compressed

pellets were ground and sieved through a 120-mesh (125μm) sieve and retained on a ~~230 mesh~~ 230-mesh (63μm) sieve.

Please amend paragraph **[00172]** as follows:

[00172] Equal amounts of Buprenorphine particles (prepared as described in Example 4 above) and stearic acid (prepared as described in Example 3) were blended and ground. The ground material was compressed in a ~~13 mm~~ 13-mm round die, with a force of 5,000 pounds for 5 minutes. Compressed tablets were ground and sieved through a ~~120 mesh~~ 120-mesh screen followed by a ~~230 mesh~~ 230-mesh screen to obtain particles having a size range between 63-125 microns.

Please amend Table 10 originally appearing on page 57 as follows:

Table 10

~~Formula~~ Formulation	P(DL)LA R202 (wt%)	BB (wt%)
51[10a]	53.1	35.4
52[10a]	57.6	31.0
53[10b]	3 Month ~~Lupron Depot®~~ LUPRON DEPOT®	

10a = 5 wt.% leuprolide acetate loaded;
10b = 3-month Lupron Depot®

Please amend paragraph **[00175]** as follows:

[00175] In general, viscosity of the depot vehicle formulations was tested using a Bohlin CVO 120 rheometer (Bohlin Instruments, Cranbury, NJ). All testing was performed at 24° C using 20 mm parallel plates. The viscosity of various gel formulations or leuprolide acetate depot formulations of the invention, as tabulated in Tables 6-12, was tested as described above. As illustrated in Figures 1, 2 and 3, the depot formulations ~~(Formulations #~~ (Formulations 42-48, 51 and 52) have different rheological properties. Thus, the depot formulations with a wide range of viscosities can be achieved by the combination of different polymers (PLGA type, molecular weight etc.), solvent or co-solvent, and different polymer/solvent ratios according to the present invention.

Please amend paragraph **[00178]** as follows:

[00178] A representative number of implantable gels were prepared in accordance with the foregoing procedures and tested for *in vitro* release of beneficial agent as a function of time. In general, the *in vitro* release of bioactive agent from the depot formulation of the present invention was performed as follows. The depot gel formulation (80-120 mg) was loaded into a tea bag and placed in a 20 mL scintillation vial and the release medium (5 mL, phosphate buffer saline (PBS) + 0.1% ~~Tween 20,~~ TWEEN® 20, pH 7.4) was added to the vial. The vial was incubated in a 37° C water bath with gentle agitation. The medium was replaced daily for the first 5 days, then twice a week thereafter until the end of the release duration. The amount of bioactive agent released from the depot was measured by various methods dependent on the nature of the bioactive agent: size exclusion chromatography high pressure liquid chromatography (SEC HPLC) is generally used for protein, while reverse phase high pressure liquid chromatography (rpHPLC) or ultraviolet (UV) techniques are generally used for small molecular compounds.

Please amend paragraph **[00181]** as follows:

[00181] A representative number of implantable gels as tabulated in Tables 4-6 were tested for in rats to determine *in vivo* release rate profiles as described in Example 15 above. In particular, depot gel hGH compositions were injected from customized 0.5 cc disposable syringes having disposable ~~16 gauge~~ 16-gauge needles, into rats and blood was drawn at specified time intervals. The release rate profile of hGH from various depot gel formulations was determined by measuring the blood serum or plasma concentrations of hGH as a function of time, as illustrated in Figures 6A-D (formulations 21, 22, 29-31, and 33-40). Samples were analyzed for intact hGH content using a radio immuno assay (RIA).

Please amend paragraph **[00182]** as follows:

[00182] A representative number of implantable gels as tabulated in Table 4 were tested for in rats to determine *in vivo* release rate profiles as described in Example 15 above. In

particular, depot gel bupivacaine compositions were injected from customized 0.5 cc disposable syringes having disposable ~~18 gauge~~ 18-gauge needles, into rats and blood was drawn at specified time intervals (1 hour, 4 hours and on days 1, 2, 5, 7, 9 and 14, 21 and 28) and analyzed for bupivacaine using LC/MS. Figures 7, 8 and 9 illustrate representative *in vivo* release profiles of bupivacaine hydrochloride (formulations 17 and 18) and bupivacaine base (formulations 19 and 20) obtained in rats from various depot formulations, including those of the present invention. The *in vivo* release profile of the depot formulations with low molecular weight PLGA (formulations 18 and 20 in Figures 7, 8 and 9) exhibited a shorter release duration of approximately 7 days, as compared to the control formulations (with higher molecular weight PLGA, formulations 17 and 19).

Please amend paragraph **[00184]** as follows:

[00184] A representative number of implantable gels as tabulated in Table 2 were tested for in rats to determine *in vivo* release rate profiles as described in Example 15 above. In particular, depot gel bupivacaine compositions were injected from customized 0.5 cc disposable syringes having disposable 18-gauge needles, into rats and blood was drawn at specified time intervals (1 hour, 4 hours and on days 1, 2, 5, 7, 9 and 14, 21 and 28) and analyzed for bupivacaine using LC/MS. Figure 12 illustrates the representative *in vivo* release profiles of bupivacaine obtained in rats from the formulations 11 and 12 (the bupivacaine depots were formulated with the PLGAs with two different molecular weight distributions in benzyl benzoate (single-modal containing MMW PLGA RG502, and bi-modal mixture of HMW PLGA RG503 with LMW PLGA, ~~Table 2~~ Table 2, formulations 11 and 12).

Please amend paragraph **[00186]** as follows:

[00186] In particular, Figure 13 illustrates representative *in vivo* release profiles of leuprolide acetate obtained in rats from depot formulations according to the present invention containing PLGA (L/G : 75/25) in either benzyl benzoate (BB) (formulation 42) or benzyl alcohol (BA) (formulation 47), as compared to a commercial 3-month leuprolide acetate depot, ~~Lupron depot®~~ LUPRON DEPOT® (formulation 53). Figure 14 illustrates representative *in vivo*

release profiles of leuprolide acetate obtained in rats from depot formulations according to the present invention containing PLGA (L/G : 75/25) in benzyl benzoate, a mixture of benzyl benzoate and benzyl alcohol, or benzyl benzoate with ethanol as a thixotropic agent (formulations 42, 43 and 45, respectively). Figure 15 illustrates representative *in vivo* release profiles of leuprolide acetate obtained in rats from depot formulations according to the present invention containing PLGA (L/G : 75/25) in benzyl benzoate with the drug particles formulated either with or without stearic acid (formulations 42 ~~& and~~ 49). Figure 16 illustrates representative *in vivo* release profiles of leuprolide acetate obtained in rats from depot formulations according to the present invention containing poly(caprolactone-co-lactic acid) (PCL-co-LA) (CL/L : 25/75) in benzyl benzoate (formulation 46) as compared to a commercial 3-month leuprolide acetate depot, ~~Lupron depot®~~ LUPRON DEPOT® (formulation 53 - from TAP ~~(The~~ (the front chamber of ~~Lupron depot®~~ LUPRON DEPOT® 3-month 11.25 mg prefilled dual-chamber syringe containing leuprolide acetate (11.25 mg), polylactic acid (99.3 mg) and D-mannitol (19.45 mg). The second chamber of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75.0 mg), polysorbate 80 (1.5 mg), water for injection, USP and glacial acetic acid, USP to control pH.)).

Please amend paragraph **[00189]** as follows:

[00189] In particular, Figure 17 illustrates representative *in vivo* release profiles of leuprolide acetate obtained in rats from depot formulations according to the present invention containing P(DL)LA in benzyl benzoate (BB) with different polymer/solvent ratios (formulations 51 and 52), as compared to the 3 month durational depot formulation (formulation 42) and a commercial 3-month leuprolide acetate depot, ~~Lupron depot®~~ LUPRON DEPOT® (formulation 53).

Please amend the section title appearing immediately before paragraph **[00191]** as follows:

Example 22

~~*InVivo*~~ *In Vivo* Release Rate Profiles of Various Buprenorphine Depot Formulations